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Oxygen reserve index guided oxygen titration in one lung ventilation with low fresh gas flow

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Background/aim: Continuous oxygen reserve index (ORI) measurement with multiple wave pulse co-oximetry is a noninvasive measurement. The decrease in the ORI trend provides a prediction for the development of hypoxemia and provides information on hyperoxia. Our aim is to determine the effect of ORI-guided oxygen titration on hyperoxemia-mediated morbidity.

Materials and methods: Consecutive 120 ASA I-III patients, 18–70 years of age, without severe obstruction or restriction, undergoing one lung ventilation (OLV), were included in the study. Patients were divided into 4 groups. Oxygen titration without ORI monitoring with low-flow anesthesia (1 L/min, Group 1, n = 25) and high-flow anesthesia (4 L/min, Group 2, n = 28). Oxygen titration by ORI monitoring with low flow anesthesia (1 L/min, Group 3, n = 25) and high flow anesthesia (4 L/min, Group 4, n = 25). FiO2 increased up to 100% if necessary. OLV time, duration of surgery and anesthesia, FiO2 applied during OLV, oxygen application time (T) over 60%, vital signs, hospital and ICU stay time, and complications were recorded.

Results: There was a statistically significant difference in terms of FiO2 used during OLV (p < 0.05). There was no difference in ORI values (p < 0.05). In Group 3, both PaO2 and SpO2 were significantly lower than the others both before and during OLV. There was no significant difference in terms of ORI parameters between low flow and high flow anesthesia groups. There was a strong, positive correlation between the duration of hospital stay and FiO2 used above 80% during OLV.

Conclusion: We concluded that ORI-guided thoracic anesthesia may reduce hospital stay and improve patient safety.

Key words: Oxygen reserve index, thoracic surgery, one lung ventilation, low flow anesthesia

1. Introduction
Oxygen saturation (SpO2) is measured by pulse oximetry during intraoperative period. Unless there is a significant decrease in PaO2 (arterial oxygen partial pressure), SpO2 may not always accurately reflect the reduction in oxygenation. Multi-wave pulse co-oximeter (Masimo, Irvine, CA, USA) and oxygen reserve index (ORI) measurement offers a noninvasive way of providing real-time visibility to oxygenation status in moderate hyperoxic range (PaO2 of approximately 100 to 200 mm Hg) [1]. ORI provides additional data on hyperoxia when SpO2 is greater than 98% [2]. The harmful effects of hyperoxemia include the formation of reactive oxygen compounds, cell damage, inflammatory pathway activation and cell death [3]. Absorption atelectasis, prolongation of hospital stays, and poor neurological activity in discharge have been reported previously [4].

One lung ventilation (OLV) is a technique used for single lung isolation to facilitate a wide variety of procedures on ipsilateral thoracic or mediastinal structures as well as to provide lung isolation. In the studies conducted to date, the importance of intraoperative hypoventilation, hyperoxemia, ventilation perfusion disorders that may occur during OLV has been mentioned [5,6]. Immediately after the onset of OLV, arterial oxygenation and saturation decrease. Accordingly, hypoxic pulmonary vasoconstriction (HPV) occurs. In order to keep SpO2 over 90% during this process, 100% oxygen (O2) is recommended [7]. Therefore, the patients are exposed to hyperoxemia.

This study aims to protect patients from the harmful effects of hyperoxemia with a noninvasive probe during OLV. The primary outcome of this study is to compare the mean FiO2 (the fraction of inspired oxygen) values in patients undergoing thoracic surgery with and without ORI monitoring. The secondary outcome is to compare the duration of 100% O2 use.

2. Materials and methods
The study was approved by the Human Research Ethics Committee of our University Medical School. Written informed consent was obtained from every patient during the preoperative visit. The study was registered in UMIN Clinical Trials Registry (UMIN000038068). This prospective, randomized, cross-sectional study included patients with lung tumors between September 2018 and September 2019. Inclusion criteria were age between 18 and 80-year-old patients undergoing elective thoracic...
surgery requiring OLV. Exclusion criteria were the refusal to participate and a history of pulmonary resection.

Patients were divided into 4 groups. Oxygen titration in the absence of ORI monitoring with low-flow anesthesia (1 L/min, Group 1, n = 25) and normal-flow anesthesia (3–4 L/min, Group 2, n = 28). Oxygen titration by ORI monitoring with low flow anesthesia (1 L/min, Group 3, n = 25) and normal flow anesthesia with ORI monitoring (3–4 L/min, Group 4, n = 25). Randomization was performed by opaque sealed envelopes.

After the patients were admitted to the operating theatre, SpO2, electrocardiogram (ECG), and noninvasive blood pressure were measured routinely. Anesthesia was induced with propofol, 2–3 mg/kg, rocuronium, 0.6 mg/kg, and fentanyl, 2–3 mcg/kg. A 20 G, radial artery catheter was placed and connected to a disposable pressure transducer following the induction of anesthesia. Tracheal intubation was performed using a left Robertshaw double lumen tube. We confirmed the position by a flexible 4.2 mm fiberoptic bronchoscope. Anesthesia maintenance was achieved with sevoflurane or desflurane, and remifentanil 0.25 mcg/kg/h.

In addition to standard follow-up parameters, ORI, noninvasive and continuous hemoglobin (SpHb), peak variable index (PVI), perfusion index (PI), and SpOc (oxygen content) were continuously monitored in Group 3 and Group 4. Patients’ SpO2, arterial oxygen partial pressure (PaO2), ORI, PVI, PI, and SpOc values were recorded and the correlation between them were determined on the continuous graphs. ORI values were measured with the Rainbow 25-L probe (Irvine, CA, USA). Patients were monitored with the Masimo low noise cabled sensors (M-LNCS) probe, which is attached to the Radical-7 Pulse CO-Oximeter device for the measurement of PVI. The duration of surgery, anesthesia, OLV, and total 100% oxygen application time were recorded. The titration of oxygen was performed manually according to the SpO2 and PaO2 values in Groups 1 and 2.

In the study groups oxygen titration was performed according to PaO2, SpO2, ORI, and SpOc values. Routine blood gas follow-ups were taken before achieving OLV, at the 15th min of OLV, 45th min of OLV. Routinely, patients were ventilated with 50% FiO2 (50% oxygen + 50% air mixture, 1 L/min fresh gas flow) after induction. FiO2 was increased to 60% when OLV is applied. Afterwards FiO2 was increased to 70%, 80%, and 100% concentration if necessary. Hemodynamic variables were recorded including heart rate and blood pressure. The incidence of thromboembolic complications, arrhythmia, pneumonia, the duration of hospital, and intensive care unit stay were recorded.

2.1. Data analysis
Study data was processed using IBM SPSS Statistics for Windows, v: 22.0 (Armonk, NY, IBM Corp.) The distribution of the variables was analyzed using the Kolmogorov–Smirnov test. The Mann–Whitney U test was used to investigate the qualitative data. The Spearman’s correlation analysis was used to examine correlation between the variables. For binary comparisons, One-way ANOVA test was used for the numerical data that conformed to the normal distribution, and the Mann–Whitney-U test was used for those who did not comply. As a 4 group comparison test, One-way ANOVA was used for the data with normal distribution and the Kruskal–Wallis test was used for those who did not comply. Chi-square test was used to analyze discrete variables. A value of p < 0.05 was considered statistically significant.

2.2. Sample size calculation
Based on a 25% reduction in the use of O2 with >60% FiO2 during OLV, it was necessary to take a total of 100 patients in this study. At a significance level of 95% the standard effect size was taken as 0.65 with a power of 90%. Therefore, a minimum of 25 patients per group were enrolled.

3. Results
A total of 103 patients aged 18 to 79 years (54.53 ± 14.46), were included in the study (Table 1). Of these patients, 27 (26.2%) were female and 76 (73.8%) were male. None of the patients were excluded. The duration of OLV with >60% FiO2 was significantly lower in ORI study groups: 67.6 ± 97.5 min, 97.32 ± 99.7 min, 39.2 ± 74.1 min and 22.4 ± 49.4 min in Groups 1–4, respectively (p = 0.003). Mean FiO2 values during OLV were 71.6 ± 12.25%, 74.64 ± 16.66%, 62.8 ± 13.08% and 56.4 ± 11.5% in Groups 1–4, respectively (p = 0.001).

The types of surgeries were VATS biopsy, VATS lobectomy, and VATS wedge resection (p = 0.085). There was no statistically significant difference between groups in terms of hemodynamic parameters (Table 2). In Group 3, both PaO2 and SpO2 were significantly lower than the others both before and during OLV (Table 3). Other blood gas parameters were similar.

There was no significant difference in terms of ORI parameters between low flow and high flow anesthesia groups. There was a strong, positive correlation between the duration of hospital stay and FiO2 used above 80% FiO2 during OLV (Table 4, p < 0.001). There was no significant relationship between the duration of intensive care unit stay and OLV with above 80% FiO2. No complication was recorded including thromboembolism, arrhythmia or pneumonia.

4. Discussion
In this study, the ORI monitor was associated with lower mean FiO2 values during OLV. With the addition of ORI monitor, lower PaO2 values were recorded. A strong significant correlation was found between the duration of OLV with above 80% FiO2 and the duration of hospital stay.

The hypoxic pulmonary vasoconstriction during OLV is characteristically biphasic. It is activated within the first few seconds in its first phase and reaches its maximum within 15 min. The second phase begins 30–40 min later and makes a late peak at the second hour. The maximal hypoxic pulmonary vasoconstriction response during OLV
reduces blood flow to the nondependent lung by 50% [6]. In this process, increasing the FiO₂ up to 1.0% and alveolar recruitment maneuvers are among the initial treatment options. However, high FiO₂ is associated with hyperoxia-induced oxidative acute lung injury [8]. Characteristics of injury are increased inflammatory-cell counts, reabsorption atelectasis, and raised pulmonary permeability, which may result in necrosis. The FiO₂ should be reduced as soon as possible. For this purpose, continuous monitoring is not possible when the analysis of blood gas parameters is intermittent. The values of the patient are recorded noninvasively with ORI measurements which is a unit-less scale. When the PaO₂ value exceeds 100 mmHg, it exceeds 0.1. In this way it is possible to protect the patient from the harmful effects of hyperoxia. ORI is a relative indicator of changes in PaO₂ in the hyperoxic range between 100 to 200 mmHg.

The use of ORI monitor is becoming increasingly common during OLV. It has been used for the determination of hypoxia; however, studies on hyperoxia are extremely limited [9]. 1.0% FiO₂ is often used during OLV. In our study, mean FiO₂ during OLV was 62.8 ± 13.08% and 56.4 ± 11.5% in patients undergoing ORI monitor. The values were 71.6 ± 12.25% and 74.64 ± 16.66% in traditionally monitored patients and were significantly higher. This result indicates that the risk of hyperoxia will be lower in patients undergoing the ORI monitor.

<table>
<thead>
<tr>
<th>Table 1. Patients' demographic and clinical characteristics.</th>
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<tr>
<td>Sex</td>
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<td>Female</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>ASA</td>
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<tr>
<td>ASA1</td>
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<tr>
<td>ASA2</td>
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<tr>
<td>ASA3</td>
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<tr>
<td>Reoperation</td>
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<tr>
<td>Complication</td>
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<tr>
<td>Duration of surgery (min)</td>
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<tr>
<td>Duration of anesthesia (min)</td>
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<tr>
<td>Duration of hospital stay (days)</td>
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<tr>
<td>Duration of OLV (min)</td>
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<tr>
<td>OLV with &gt;60% FiO₂ (min)</td>
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<tr>
<td>Mean FiO₂ during OLV (%)</td>
</tr>
<tr>
<td>Perioperative colloid (mL)</td>
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<td>Perioperative crystalloid (mL)</td>
</tr>
</tbody>
</table>

* Chi-square test: values are given as frequency (percentage).
* Kruskal-Wallis H test: values are given as mean ± standard deviation.
* One-way Anova test: values are given as mean ± standard deviation.
* p < 0.05 statistically significant.
A = G2 vs. G3, p = 0.005; G2 vs. G4, p = 0.011.
B = G1 vs. G3, p = 0.019; G1 vs. G4, p = 0.001; G2 vs. G3, p = 0.006; G2 vs. G4, p = 0.001; G3 vs. G4, p = 0.021.
Group 1: Low-flow anesthesia and oxygen titration without ORI monitoring.
Group 2: Normal-flow anesthesia and oxygen titration without ORI monitoring.
Group 3: Low-flow anesthesia and oxygen titration with ORI monitoring.
Group 4: Normal-flow anesthesia and oxygen titration with ORI monitoring.
Table 2. Hemodynamic parameters, SpO₂, etCO₂ and temperature variables of patients before and during OLV.

<table>
<thead>
<tr>
<th></th>
<th>Before OLV</th>
<th>15 min after OLV</th>
<th>45 min after OLV</th>
<th>At the end of OLV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 25)</td>
<td>Group 2 (n = 28)</td>
<td>Group 3 (n = 25)</td>
<td>Group 4 (n = 25)</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>73.87 ± 13.67</td>
<td>79.82 ± 10.36</td>
<td>83.08 ± 16.4</td>
<td>82.64 ± 20.24</td>
</tr>
<tr>
<td><strong>Heart rate (beat/min)</strong></td>
<td>68.72 ± 12.71</td>
<td>74.57 ± 14.95</td>
<td>73.4 ± 13.37</td>
<td>87.4 ± 99.73</td>
</tr>
<tr>
<td><strong>SpO₂ (%)</strong></td>
<td>99.08 ± 1.85</td>
<td>99.46 ± 0.69</td>
<td>98.16 ± 1.72</td>
<td>98.6 ± 1.41</td>
</tr>
<tr>
<td><strong>etCO₂ (mmHg)</strong></td>
<td>34.68 ± 3.57</td>
<td>34.54 ± 3.99</td>
<td>33.58 ± 3.68</td>
<td>34.25 ± 3.45</td>
</tr>
<tr>
<td><strong>Temperature (°C)</strong></td>
<td>35.64 ± 1.0</td>
<td>35.78 ± 0.68</td>
<td>35.80 ± 0.60</td>
<td>35.79 ± 0.72</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>73.08 ± 11.85</td>
<td>75.96 ± 8.58</td>
<td>77.56 ± 11.19</td>
<td>74.84 ± 8.61</td>
</tr>
<tr>
<td><strong>Heart rate (beat/min)</strong></td>
<td>72.44 ± 11.72</td>
<td>74.14 ± 12.25</td>
<td>74.56 ± 15.98</td>
<td>68.64 ± 10.64</td>
</tr>
<tr>
<td><strong>SpO₂ (%)</strong></td>
<td>97.72 ± 5.37</td>
<td>97.46 ± 1.77</td>
<td>94.84 ± 11.8</td>
<td>96.48 ± 2.2</td>
</tr>
<tr>
<td><strong>etCO₂ (mmHg)</strong></td>
<td>33.68 ± 4.05</td>
<td>34.03 ± 3.74</td>
<td>38.21 ± 12.63</td>
<td>34.64 ± 3.56</td>
</tr>
<tr>
<td><strong>Temperature (°C)</strong></td>
<td>35.39 ± 1.0</td>
<td>35.44 ± 0.27</td>
<td>35.63 ± 0.76</td>
<td>35.35 ± 0.79</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>73.54 ± 9.04</td>
<td>79.39 ± 9.52</td>
<td>74.19 ± 12.15</td>
<td>77.63 ± 7.35</td>
</tr>
<tr>
<td><strong>Heart rate (beat/min)</strong></td>
<td>69.63 ± 12.15</td>
<td>74 ± 11.43</td>
<td>70 ± 11.04</td>
<td>65.83 ± 7.94</td>
</tr>
<tr>
<td><strong>SpO₂ (%)</strong></td>
<td>98.21 ± 1.67</td>
<td>97.36 ± 1.95</td>
<td>95.73 ± 2.41</td>
<td>97.46 ± 2.23</td>
</tr>
<tr>
<td><strong>etCO₂ (mmHg)</strong></td>
<td>33.21 ± 4.76</td>
<td>33.36 ± 3.55</td>
<td>33.68 ± 3.18</td>
<td>33.92 ± 3.64</td>
</tr>
<tr>
<td><strong>Temperature (°C)</strong></td>
<td>35.3 ± 0.99</td>
<td>35.23 ± 0.67</td>
<td>35.27 ± 0.60</td>
<td>35.2 ± 0.77</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>73.77 ± 12.9</td>
<td>79.71 ± 10.06</td>
<td>81.27 ± 9.06</td>
<td>80.25 ± 8.08</td>
</tr>
<tr>
<td><strong>Heart rate (beat/min)</strong></td>
<td>70.78 ± 12.26</td>
<td>75.61 ± 11.91</td>
<td>73.55 ± 13.45</td>
<td>67.33 ± 6.85</td>
</tr>
<tr>
<td><strong>SpO₂ (%)</strong></td>
<td>98.57 ± 2.13</td>
<td>98.86 ± 1.65</td>
<td>97.77 ± 2.16</td>
<td>98.54 ± 1.22</td>
</tr>
<tr>
<td><strong>etCO₂ (mmHg)</strong></td>
<td>33.43 ± 5.18</td>
<td>34.57 ± 9.89</td>
<td>33.23 ± 3.25</td>
<td>34.71 ± 3.76</td>
</tr>
<tr>
<td><strong>Temperature (°C)</strong></td>
<td>35.41 ± 1.0</td>
<td>35.37 ± 0.77</td>
<td>35.15 ± 0.65</td>
<td>35.06 ± 0.75</td>
</tr>
</tbody>
</table>

*<sup>p < 0.05</sup> Statistically significant between groups.

<sup>a</sup> One-way Anova test: values are given as mean ± standard deviation.

<sup>b</sup> Kruskal-Wallis H test: values are given as mean ± standard deviation.

A₁ = G1 vs. G3, p = 0.012; G2 vs. G3, p = 0.003; G2 vs. G4, p = 0.021.

A₂ = G1 vs. G3, p = 0.001; G2 vs. G3, p = 0.001; G3 vs. G4, p = 0.013.

Group 1: Low-flow anesthesia and oxygen titration without ORI monitoring.
Group 2: Normal-flow anesthesia and oxygen titration without ORI monitoring.
Group 3: Low-flow anesthesia and oxygen titration with ORI monitoring.
Group 4: Normal-flow anesthesia and oxygen titration with ORI monitoring.
Arterial blood gas analysis is essential for the management of patients. However, it is not a continuous monitoring method and besides takes a long time. We obtained real time data with the ORI monitor. Thus it was possible to detect changes in pulmonary function. As Campos and Sharma [10] mentioned, ORI cannot replace arterial blood gases analysis, however it is useful to assess oxygenation. In groups without ORI monitors, the FiO2 was significantly higher than 80%. Moreover, in our study, it was revealed that these patients had a longer hospital stay.

Koishi et al. [11] showed in their 15 subjects that ORI and PaO2 were highly correlated during OLV. However, in 13 of the 15 cases, PaO2 was >240 mmHg at the start of

<table>
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<th>Table 3. The comparison of blood gas parameters.</th>
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<tr>
<td>Before OLV</td>
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<tr>
<td>(n = 25)</td>
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<tr>
<td>Ph</td>
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<tr>
<td>CO2 (mmHg)</td>
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<tr>
<td>PaO2 (mmHg)</td>
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<tr>
<td>SpO2 (%)</td>
</tr>
<tr>
<td>Base excess</td>
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<tr>
<td>Lactate</td>
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<tr>
<td>15 min after OLV</td>
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<tr>
<td>(n = 25)</td>
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<tr>
<td>Ph</td>
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<tr>
<td>CO2 (mmHg)</td>
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<td>PaO2 (mmHg)</td>
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<td>SpO2 (%)</td>
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<tr>
<td>Base excess</td>
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<tr>
<td>Lactate</td>
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<tr>
<td>45 min after OLV</td>
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<tr>
<td>(n = 25)</td>
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<tr>
<td>Ph</td>
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<tr>
<td>CO2 (mmHg)</td>
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<td>PaO2 (mmHg)</td>
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<td>SpO2 (%)</td>
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<td>Base excess</td>
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<td>Lactate</td>
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<tr>
<td>At the end of OLV</td>
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<td>CO2 (mmHg)</td>
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<tr>
<td>Base excess</td>
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<tr>
<td>Lactate</td>
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</tbody>
</table>

A1 = G1-G2, p = 0.023 vs. G1-G3, p = 0.001 vs. G1-G4, p = 0.003 vs. G2-G3, p = 0.030.
A2 = G1-G3, p = 0.002 vs. G2-G3, p = 0.004.
A3 = G1-G3, p = 0.005 vs. G2-G3, p = 0.027 vs. G3-G4, p = 0.009.
A4 = G1-G3, p = 0.019 vs. G2-G3, p = 0.014.
B1 = G1-G3, p = 0.001 vs. G1-G4, p = 0.028 vs. G2-G3, p = 0.001 vs. G2-G4, p = 0.018.
B2 = G1-G3, p = 0.002 vs. G1-G4, p = 0.029 vs. G2-G3, p = 0.005.
*p < 0.05 statistically significant between groups.
Group 1: Low-flow anesthesia and oxygen titration without ORI monitoring.
Group 2: Normal-flow anesthesia and oxygen titration without ORI monitoring.
Group 3: Low-flow anesthesia and oxygen titration with ORI monitoring.
Group 4: Normal-flow anesthesia and oxygen titration with ORI monitoring.
OLV. Applegete et al. [12] concluded that when SpO₂ is >98%, ORI can distinguish PaO₂ between 100 and 150 mm Hg. The main difference of our study was the prevention of patients from hyperoxemia with the ORI monitor. The harmful effects of oxygen were eliminated by titrating the oxygen. There was a strong, positive correlation between the duration of hospital stay and FiO₂ used above 80% during OLV. There was no significant relationship between the duration of Intensive Care Unit stay and OLV with above 80% FiO₂.

Exaggerated perioperative inflammatory response in patients undergoing lung resection surgery has been shown to potentially increase the risk of postoperative pulmonary complications [6]. Also, patients undergoing thoracic surgery are at risk of hypoxemia and hypercarbia due to their existing disease. Besides one lung ventilation may cause ventilation perfusion rate changes and devastating effects due to mechanical ventilation [13]. In the present study we revealed that low flow anesthesia can be safely used during one lung ventilation. Using the ORI monitor, we had no complications.

4.1. Limitations
In this study, malignant and benign patients were studied together. The fact that only patients with malignancy were not included in the study might have had an impact on the length of stay in the hospital or ICU. This was the most important limitation of the study. Studying in larger sample size, might have increased the reliability of the study.

4.2. Conclusion
The adjustment of Ori with peripheral oxygen saturation and blood gas analysis demonstrated that hyperoxemia could be prevented during OLV in patients under low flow or high flow anesthesia. We concluded that ORI-guided thoracic anesthesia may reduce hospital stay and increase patient safety.

Acknowledgment
The authors state no conflict of interest.

Conflict of interest
The authors declare that there is no conflict of interest.

Informed consent
The study protocol received institutional review board approval (approval code: 09.2018.141, date: 02.02.2018) and all participants provided informed consent in the format required by the relevant authorities and/or boards.

References
